REMARKS

The present application features methods for reducing a neurological deficit in a patient who has suffered an injury to the central nervous system. In the methods claimed, an epidermal growth factor-like (EGF-like) polypeptide (*e.g*, EGF) is administered to the patient after a certain period of time has passed (*e.g.*, administration can begin six hours after the injury).

Claims 1-6, 17, 18, and 25-43 are pending in the application. Claims 7-16 and 19-24 are canceled. Claim 38 has been amended to depend from claim 36, instead of claim 37. No new matter has been added.

Claim Objection

The Examiner objected to claim 38 "...under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim" (Office action at page 2). In response, Applicant amended claim 38 to depend from claim 36 instead of claim 37. Claim 36 recites "an ischemic episode," and amended claim 38 recites "a global ischemic episode." As amended, claim 38 limits the subject matter of claim 36, and thus the amended claim satisfies 37 C.F.R. §1.75(c). In light of the amendment, Applicant requests that the objection to claim 38 be withdrawn.

35 U.S.C. §103

The Examiner rejected all of the pending claims (claims 1-6, 17, 18, and 25-43) as being obvious over Reynolds *et al.* (WO 98/21127; herein, "Reynolds") in view of Peng *et al.* (*J. Cerebral Blood Flow and Metabolism* 18:349-360, 1998; herein, "Peng").

This ground for rejection is respectfully traversed. Applicants maintain that there is no *prima facie* case of obviousness.

Before presenting specific comments concerning Reynolds and Peng, Applicant reviews relevant passages from the MPEP concerning rejections based on obviousness. First, regarding the initial burden, the MPEP states, "[t]he examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." MPEP at 2142. Moreover, "[t]o reach a

proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." MPEP at 2142. The MPEP then goes on to review the basic requirement that must be met in order for the Examiner to establish a *prima facie* case of obviousness. At 2143, the MPEP states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USQP2d 1438 (Fed. Cir. 1991).

The MPEP also reminds Examiners of their responsibility to apply "the standard of patentability enunciated by the Supreme Court" in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966). MPEP at 2141. In *Graham*, the Supreme Court stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

In view of the requirements and standards reviewed above, we turn to the facts of the present case.

Applicant's claims are limited to a particular treatment regime, one in which an EGF-like polypeptide is administered commencing (*i.e.*, beginning) more than 6, 12, or 24 hours after an injury to the central nervous system (CNS; *see* independent claims 1, 26, and 35, respectively). The Examiner recognizes that neither Reynolds nor Peng teach or suggest such a treatment regime. The Examiner states, "[w]hile it is true that administration of EGF in experiments of Peng et al. did not commence 6, 12, or 24 hours after the injury, it continued during and long after these particular time points" (Office action at page 3). Similarly, with respect to Reynolds, the Examiner states, "Reynolds et al. do not expressly disclose a method of administration of

EGF for reducing a neurological deficit in a patient with an injury to the CNS wherein administration of EGF commences more than 6, 12, or 24 hours after the injury" (Office action at pages 4-5). As the present claims *are* limited to administration beginning more than 6, 12, or 24 hours after the injury, and as neither Reynolds nor Peng suggest such a method, neither Reynolds nor Peng teach or suggest all the limitations of the methods now claimed. With all due respect, it is irrelevant that the prior methods might encompass the time periods recited in Applicant's claims; despite an overlap, the prior methods are not limited in the way the methods now claimed are limited. As noted above, to establish a *prima facie* case of obviousness, the prior art reference(s) must teach or suggest all the claim limitations. That requirement is simply not met here. On that basis alone, the rejection for obviousness should be withdrawn.

Moreover, neither Reynolds nor Peng suggest that their treatment regimes should be modified (to the contrary!), and there is no reasonable expectation for success.

Reynolds and Peng both aimed to prevent neuronal cell death, which is known by those of ordinary skill in the art to occur rapidly (often within minutes) following an ischemic episode. Neurons are known to be especially sensitive to oxygen deprivation. Reynolds states that his methods are aimed at "*protecting* mammalian neural tissue from trauma or insult" (page 4, line 1; emphasis added) and his Figure 1 demonstrates that EGF *pretreatment* can protect against ischemia-induced *cell death* in the CA1 region of the hippocampus" (page 5, lines 1-2; emphasis added). Similarly, Peng's treatment began prior to or immediately after transient forebrain ischemia and "effectively prevented delayed *neuronal death* of CA1 neurons" (Abstract; emphasis added). Thus, both Reynolds and Peng taught that treatment should begin before or immediately after a CNS injury in order to prevent neurons within the CNS from dying. There is no suggestion that these prophylactic treatment regimes should be modified so that that EGF (or an EGF-like polypeptide) is administered well after neurons within the CNS have died – as the present Applicant now claims. As there must be some suggestion or motivation to modify the reference before there can be a *prima facie* case of obviousness, and as there is no such suggestion here, there can be no *prima facie* case of obviousness. Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection.

The fact that Peng suggests a "neuroprotective" effect does not provide the requisite motivation. The Examiner states, "[t]here is no scientific evidence to support the conclusion that such effect is only achieved by administration of EGF before free radical neurotoxicity and lipid peroxidation occur" (Office action at pages 3-4). By way of this statement, the Examiner seems to be requesting a teaching away. But the law does not require the prior art to show or suggest that that no other treatment regime would work. Peng does not have to state, in effect, that EGF would not be effective if it were administered later. Regardless of any mechanism discussed in the Peng publication, it is clear that Peng advocated treatment prior to or immediately after a CNS injury in order to protect neurons from dying, and there is no motivation to modify that treatment, let alone to modify it in such a way that administration would not begin until long after neurons have died.

Finally, there is no expectation for success. The Examiner's attention is directed to the article that appeared in the Boston Globe on February 5, 1999 (well after the present application was filed). That article (see **Tab A**) supports the Applicant's position that one of ordinary skill in the art would not have expected that treatment more than six hours following an injury to the CNS would be successful. One such injury, a stroke, typically results in damage or death of neurons of the CNS, which in turn leads to motor and cognitive defects in the patient. Concerning strokes, the Globe article states (emphasis added):

> For the first time, doctors have shown that they can reverse massive strokes as many as six hours after symptoms arise...The new approach offers potentially better treatment for the worst strokes and a doubling of the three hour window for treating stroke victims before they suffer permanent damage...[emphasis added]

Thus, in February 1999, the longest known treatment window was reported to be three hours; extension of that window to six hours (as Applicant had previously claimed) was considered a new and ground breaking (or, at least, news worthy) event. Prior to that time, there was no reason to expect that Applicant's method would succeed. There is certainly nothing in Reynolds or Peng to suggest that one of ordinary skill in the art could have expected success.

The medical profession has long believed that the key to treating CNS injuries is to act as quickly as possible after the injury occurs in an attempt to prevent damage to, and death of, neurons. This is consistent with the experiments Reynolds and Peng performed. Moreover, even in 2000 (one year after the Globe article was published), the American Stroke Association was characterizing stroke as a "medical emergency" (see **Tab B**; 08/10/2000 printout of www.strokeassociation.org, page 1). Journal papers and news releases from the same year supported the view that stroke treatment must be immediate and, therefore, delayed treatment regimes are unlikely to succeed. For example, a news release on the American Stroke Association website stated, "[a] critical step in surviving a stroke – which is the blockage of blood flow to the brain caused by a clogged or ruptured blood vessel – is speed. Call 911 as soon as the signs are evident" (see **Tab C**; 05-02-2000, ASA News Release).

As the references cited by the Examiner fail to suggest delayed treatment of an injury to the CNS, they cannot but fail to suggest that such treatment would succeed. Here again, the fact that Reynolds or Peng may have continued their treatment to, and even beyond, Applicant's starting point, is of no consequence. Starting a treatment before or soon after an injury to the CNS and continuing that treatment for any length of time (whether that be days, weeks, or months) is very different from delaying the onset of the treatment until well after neurons within the CNS have died (as Applicant now claims). Given the failure of Reynolds and Peng to suggest the methods now claims, particularly in view of the widely publicized and well accepted belief that injuries to the CNS must be treated as soon as possible, one of ordinary skill in the art would have no reason to expect that delayed treatment – as Applicant now claims – would succeed. Accordingly, there can be no *prima facie* case of obviousness. The Examiner is respectfully requested to reconsider and withdraw this ground for rejection.

CONCLUSION

In view of the arguments presented above, Applicant contends that the present claims are now in condition for allowance, which action is respectfully requested. Should the Examiner

find the present remarks unpersuasive, Applicant's representative hereby requests a telephone interview to discuss any remaining issues.

Enclosed is a Petition for Extension of Time and a check in the amount of $1,005 for the associated fee. If there are any other charges, or any credits, please apply them to Deposit Account No. 06-1050, referencing Attorney Docket No. 00786-400002.

Respectfully submitted,

Date: November 24, 2003

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National Briefs

Abortion foe vows to film patients

ATLANTA – A man who runs an antiabortion Web site said yesterday that he plans to identify women who obtain abortions by displaying live video of them entering clinics in the United States, Britain, and Japan. "We'll film people going in and out of the clinics. We'll film the faces of people who are entering and the faces of mothers driving their daughters to clinics to have abortions," Neal Horsley, who runs the Internet site, said. But a spokesman for Planned Parenthood said any attempt to videotape women at clinics would face legal action. (Reuters)

Drug found to add to 3-hour stroke therapy window

ASSOCIATED PRESS

NASHVILLE – For the first time, doctors have shown that they can reverse massive strokes as many as six hours after symptoms arise, by squirting a clot-dissolving medicine directly into the brain.

The new approach offers potentially better treatment for the worst strokes and a doubling of the three-hour window for treating stroke victims before they suffer permanent brain damage.

Doctors tested the agent, called prourokinase, on people who had suffered a particularly serious form of stroke that accounts for about one-third of the 600,000 strokes treated in the United States annually.

"If you have a massive stroke, this gives you the best chance of a decent outcome," said Dr. Steven R. Levine of Detroit Medical Center, who was not involved in the study.

Until two years ago, strokes were untreatable in the hours immediately after they occurred. Then researchers discovered that TPA, or tissue plasminogen activator, a mainstay in treating heart attacks, could dissolve the blood clots that cause most strokes.

But research suggested that TPA could help only if given within three hours of the start of symptoms, such as numbness and difficulty talking, and if a brain scan had determined that the stroke resulted from a clot. Even then, there was about a 6 percent chance that TPA would trigger bleeding that made the stroke worse.

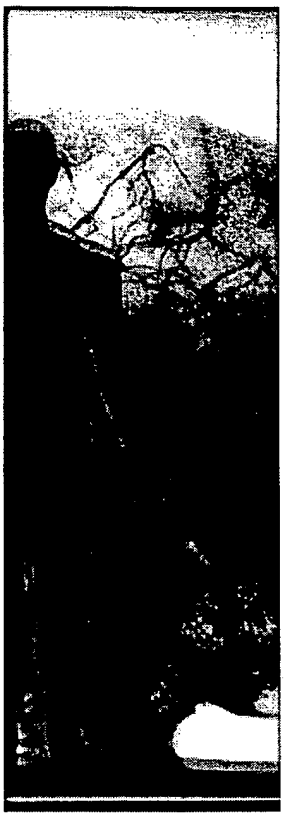
The results of the prourokinase study, directed by Dr. Anthony J. Furlan of the Cleveland Clinic Foundation, were released yesterday at a stroke conference sponsored by the American Heart Association. The study was financed by Abbott Laboratories, which is developing the drug.

Prourokinase may be more effective because it is released via a catheter, threaded through an artery, directly into the brain. TPA is injected into a vein and must travel through the body.

American Stroke Association
A Division of American Heart Association

Who We Are | Consumer | Professional | Media | How Can I Help? | Home | Americanheart.org

Find out how you can join the challenge to reduce strokes. american STROKE challenge



Stroke is A Medical Emergency CALL 911!

Know the warning signs!

- Sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- Sudden confusion, trouble speaking or understanding
- Sudden trouble walking, dizziness, loss of balance or coordination
- Sudden trouble seeing in one or both eyes
- Sudden severe headache with no known cause

Every 53 seconds, someone in America has a stroke. About 600,000 Americans will have a stroke this year – and 160,000 of them will die. In fact, stroke is our nation's No. 3 killer, and one of the leading causes of disability. But we are fighting back. The American Heart Association spends more on stroke-related research, and stroke-related programs than any other non-profit organization, second only to the federal government. In November 1998, the American Heart Association made the decision to rename its Stroke Division. It is now the American Stroke Association...A Division of the American Heart Association.

Who We Are
Learn more about the history of stroke within the American Heart Association and how we became who we are today.

Consumer
Educate yourself about stroke prevention, treatment and services available to stroke survivors.

Professional
Find information about research grants, scientific statements, conferences and other products and services for medical professionals.

Media
News and information about stroke and the American Stroke Association.

How Can I Help?
Find out how to get more involved in the fight against stroke.

American Stroke Association

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ASA News Releases

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FOR IMMEDIATE RELEASE

Mother's Day Advice That Could Save Her Life

Share Life-Saving Information to Celebrate Mother's Day and Stroke Awareness Month

(DALLAS) - May is Stroke Awareness Month. May 14 is Mother's Day. That's a good combination, according to the American Stroke Association, because it draws attention to a sad fact - stroke kills more than 97,000 women each year - and an encouraging fact - you can help reduce those numbers.

That's why taking the time to learn the warning signs this month could be the best Mother's Day present you could ever give anyone. It can make the difference between life and death.

A critical step in surviving a stroke - which is a blockage of blood flow to the brain caused by a clogged or ruptured blood vessel - is speed. Call 911 as soon as the signs are evident.

Fast action is important, especially now that a new emergency treatment for stroke - a clot-busting drug called tissue plasminogen activator (t-PA) - can greatly reduce the risk of death and permanent damage. Unfortunately, less than 5 percent of Americans get to the hospital in time to receive t-PA, which must be administered within three hours of the onset of symptoms to be effective.

"If more stroke patients knew the warning signs for stroke and arrived at the hospital in time for treatment, we could decrease the number of people who die or are permanently disabled by stroke," said American Stroke Association volunteer Harold P. Adams, Jr., M.D. from the Univeristy of Iowa.

The warning signs of stroke are:

- sudden weakness or numbness of the face, arm or leg, especially on one side of the body;
  sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden trouble walking, dizziness, loss of balance or coordination;

- sudden severe headache with no known cause.

According to the American Stroke Association, the medical outcome of a stroke patient who receives the clot-busting drug and a patient who doesn't get to the hospital in time for treatment can be dramatically different. One grandmother could have the ability to carry their grandbaby in a few days, while the other might never regain her strength.

More than half of women who survive a stroke die within eight years. However, the chance of suffering a stroke can be reduced by practicing a healthy lifestyle.

Women should control high blood pressure, stop smoking, control blood cholesterol, become physically active, avoid obesity and work with a doctor to prevent or treat atrial fibrillation and carotid artery disease. Atrial fibrillation is the rapid, uncoordinated beating of the heart's upper chambers. Carotid artery disease affects the blood vessel system that supplies the brain.

The American Stroke Association, a division of the American Heart Association, was created in November 1998 as part of a strategic decision to spotlight and strengthen the American Heart Association's effort to reduce death and disability from stroke through research, education, fundraising and advocacy.

To learn more about stroke, including the warning signs, prevention and risk assessment, call **1-888-4-STROKE** or visit the American Stroke Association Web site at www.StrokeAssociation.org.